Endogenous pain facilitation rather than inhibition differs between people with chronic fatigue syndrome, multiple sclerosis, and controls: an observational study

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ABSTRACT

Background: Commonalities in the core symptoms of fatigue and cognitive dysfunction experienced by chronic fatigue syndrome (CFS, also known as 'ME') and multiple sclerosis (MS) patients have been described. Many CFS and MS patients also experience chronic pain, which has been attributed to central sensitization in both groups of patients. However, the characteristics of pain in CFS and MS patients have not been compared.

Objectives: To compare experimental pain measurements in CFS and MS patients and healthy controls.

Study design: Observational study

Setting: This study took place in Belgium at Vrije Universiteit Brussel and the University of Antwerp.

Methods: Pressure pain thresholds, temporal summation, conditioned pain modulation, and occlusion cuff pressure thresholds rated as painful (1st cuff pressure threshold) and as 3/10 on verbal numerical scale (2nd cuff pressure threshold) were measured in CFS patients (n=48), MS patients (n=19) and healthy pain-free controls (n=30). Adjusted between-group differences were estimated using linear regression models.

Results: Finger pain pressure thresholds of CFS patients, compared with MS patients, were 25% lower (difference ratio 0.75 (95% CI 0.59, 0.95), p=0.02) and shoulder pain pressure thresholds were 26% lower (difference ratio 0.74 (0.52, 1.04), p=0.08). Compared with MS patients, CFS patients had 29% lower 1st cuff pressure threshold (difference ratio 0.71 (0.53, 0.94), p=0.02) and 41% lower 2nd cuff pressure threshold (0.59 (0.41, 0.86), p=0.006). Finger temporal summation was higher in CFS than in MS patients (mean difference 1.15

(0.33, 1.97), p=0.006), but there were no differences in shoulder temporal summation or conditioned pain modulation at either site. Differences between CFS and MS patients tended to be greater than between either patient group and healthy controls. pain pressure thresholds and cuff pressure thresholds tended to be positively correlated, and temporal summation negatively correlated, with higher physical function and lower fatigue in both groups of patients. Subjective pain in CFS but not in MS patients was strongly negatively correlated with pain pressure thresholds and cuff pressure thresholds, and positively correlated with temporal summation.

Limitations: The main limitations of our study are the relatively small sample sizes, its cross-sectional design, and its exploratory nature.

Conclusions: We found differences in the characteristics of pain symptoms reported by CFS and MS patients, which suggest different underlying mechanisms. Specifically, overactive endogenous pain facilitation was characteristic of pain in CFS but not in MS patients, suggesting a greater role for central sensitization in CFS.

Keywords: chronic fatigue syndrome; CFS/ME; multiple sclerosis; experimental pain; central sensitization

INTRODUCTION

Chronic fatigue syndrome (CFS), also known as 'myalgic encephalomyelitis' (ME), is characterized by persistent or recurrent debilitating fatigue that is not explained by other conditions, and that results in a substantial reduction in daily activity (1). Almost all CFS patients present with the three cardinal symptoms of post-exertional malaise, cognitive dysfunction and disturbed/unrefreshing sleep, one fifth of adult CFS patients also present with muscle and joint pain as predominant symptoms (2), and approximately one third have co-morbid fibromyalgia (FM) (3).

Multiple sclerosis (MS) is an inflammatory demyelinating disease of the central nervous system, manifesting as a neurological disorder in adults. Fatigue, cognitive dysfunction and pain are three of the most common MS symptoms, with significant impact on overall quality of life (4-6). Two thirds of MS patients report fatigue as being one of the most debilitating symptoms of the disease (7), 45–65% of patients with MS exhibit cognitive deficits on clinical assessment (8), and a similar proportion experience pain (9).

Commonalities in the core symptoms experienced by CFS and MS patients have prompted a wide range of studies in which characteristics of the two patient groups have been compared. The motivation for these studies is that MS is a disease of known neurologic pathology, whereas there are few, if any, clues as to aetiopathology of CFS. Similarities and differences in pain experienced by CFS and MS patients have yet to be explored as a potential means of gaining insight into the causal background of pain symptoms. In particular, central sensitization, i.e. increased excitability of the central nervous system, has been demonstrated in CFS (10,11), and has been posited to play a role in MS, albeit on the basis of one study which reported widespread hyperalgesia in MS patients (12). Central sensitization is characterized by impaired endogenous pain inhibition (13) and overactive endogenous pain facilitation (14). If central sensitization explains part of the pain experienced by patients with

MS, then these patients should present with poorer functioning of endogenous pain inhibition and/or overactive endogenous pain facilitation.

In this study we measured widespread pressure hyperalgesia, deep tissue hyperalgesia, endogenous pain facilitation, and endogenous pain inhibition in CFS and MS patients and healthy pain-free controls. We also investigated whether there were any between-group differences in the relationships between these experimental pain measures and self-reported patient characteristics. We hypothesized that patients with CFS and MS, compared to controls, would present with poorer functioning of endogenous pain inhibition and/or with overactive endogenous pain facilitation. In addition, if these mechanisms contribute to the pain experience in people with CFS and/or MS, then we would expect the corresponding pain measurements to be associated with clinical characteristics of CFS and MS patients, such as fatigue, physical and mental function, and overall health status.

METHODS

Study design and setting

This blinded observational study took place at the Pain in Motion research labs in Antwerp and Brussels. The study was approved by the ethics committees of the University Hospital Brussels/Vrije Universiteit Brussel and the University Hospital Antwerp, and written informed consent was obtained from all participants prior to commencement of the study.

Participants

General eligibility

All study participants had to be Dutch speaking and aged 18-65 years. To preclude confounding factors, participants could not suffer from intellectual disabilities and women could not be pregnant or <12 months postnatal. Participants were asked to stop anti-depressive, anti-epileptic and opioid pain medication two weeks prior to study participation,

and not to undertake physical exertion and to refrain from taking analgesics and consuming caffeine, alcohol or nicotine on the days of the assessments.

CFS patients

Patients with CFS were recruited from a practice for internal medicine in Ghent (Belgium), through advertisements placed in the newsletter of a local patient support group, and during pain information sessions which are held on behalf of patient support groups. Written confirmation of a CFS diagnosis as defined by the United States Centres for Disease Control and Prevention (CDC) 1994 criteria for CFS was required from each participant's physician (1).

MS patients

Patients fulfilling the McDonald diagnostic criteria for MS (15) were recruited through the neurology department of the University Hospital of Antwerp. All patients were recruited via a specialist neurologist who had extensive experience in the diagnosis and treatment of MS. Patients had to have an Expanded Disability Status Scale (EDSS) score <6 (16) and to be relapse free in the last 3 months. No constraints were placed on type of MS.

Healthy controls

Healthy [pain-free and without any (chronic) disease] inactive control persons were recruited from among relatives, friends or acquaintances of researchers, students, university personnel or study participants. "Inactive" was defined as working in an occupation that did not require moderate to intense physical labour and performing a maximum of three hours of moderate physical activity/week. Moderate physical activity was defined as activity demanding at least three times the amount of energy expended passively (17).

Assessments and measurements

The study comprised two standardized assessment sessions separated by seven days. All assessments were performed by the same researchers who were blinded to whether participants were patients or controls. Informed consent and baseline clinical and demographic characteristics were collected at the first assessment. Seven days later, muscle strength and recovery and experimental pain measurements were made, and participants were asked to complete a range of questionnaires.

Patient-reported measures (questionnaires)

Overall health status

The Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36) is a health-related quality of life (HRQOL) instrument composed of 8 multi-item scales which can be aggregated into two summary measures: the Physical (PCS) and Mental (MCS) Component Summary scores (18). Higher scores represent better health. The SF-36 is one of the most frequently used patient-reported measures in the assessment of adults with CFS (19).

Fatigue

The Checklist Individual Strength (CIS) contains 20 items which measure 4 dimensions of fatigue: (1) subjective fatigue severity; (2) reduced concentration; (3) reduced motivation; (4) reduced physical activity (20). Respondents indicate, on a 7-point Likert scale, the degree to which each item was true for them in the 2 weeks preceding the assessment. Higher scores represent a higher level of fatigue and lower levels of concentration, motivation, and physical activity. The CIS has good discriminative validity, and its four dimensions have excellent consistency (Cronbach's α 0.83-0.92) (20,21).

Depression

The Beck Depression Inventory for Primary Care (BDI-PC) is a 7-item instrument used for the assessment of depressive symptoms. Each item contains 4 statements, and respondents are asked to indicate the statement that best suits their feelings for the past 2 weeks including

today. Within each item statements are rated on a 4-point scale ranging from 0 to 3. The BDI-PC is scored by summing all of the highest ratings for each item (maximum score 21). The BDI-PC has high internal-consistency (Cronbach's α of 0.85) (22).

Self-reported pain severity

The CFS Symptom List (23), comprising visual analogue scales (100 mm) for 19 of the most common CFS symptoms, was used to obtain a subjective measure of current levels of pain.

Experimental pain measurements

Widespread pressure hyperalgesia: pressure pain thresholds

Pressure pain thresholds were measured at the middle of the right trapezius belly (shoulder pain pressure threhold) and at the dorsal surface of the right hand middle finger midway between the first and second distal joint (finger pain pressure threshold) with an analogue Fisher algometer (Force Dial, Wagner Instruments, Greenwich CT, USA) (24). Participants' pain pressure thresholds were determined by increasing the pressure provided by the algometer (at a rate of 1kg/s) until the point the sensation first became painful (participants were instructed to say 'stop' at this point). This was performed twice (30s apart) at the shoulder and at the finger in order to calculate the mean pain pressure threshold for each site. Pressure algometry has been found to be efficient and reliable in the exploration of pathophysiological mechanisms involved in pain (25).

Deep-tissue hyperalgesia: occlusion cuff pressure

Cuff pressure thresholds were assessed by inflating an occlusion cuff placed around the left arm. The cuff served as the conditioning stimulus in the conditioned pain modulation measurement. Cuff inflation was increased manually and at a constant rate (20mmHg/s) until the participant reported the sensation becoming painful - participants were instructed to say 'stop' – and the pressure at this point was recorded as '1st cuff pressure threshold'. Participants then adapted to the stimulus for 30 seconds and rated the pain on a verbal

numerical rating scale (VNRS) ranging from 0 (no pain) to 10 (worst possible pain). Cuff inflation was then adjusted until participants indicated pain at a level 3/10 on the VNRS, and the pressure at this point was recorded as ’2nd cuff pressure threshold’.

Endogenous pain facilitation: temporal summation

Temporal summation was examined 2min after the final pain pressure threshold was taken at each site (finger and shoulder). Participants were given ten pulses to the previously determined mean pain pressure threshold intensity and this pressure was maintained for 1s before being released. Pressure was increased, from zero until the predetermined intensity, at a rate of approximately 2kg/s for each pulse and pulses were presented with an interstimulus interval of 1s. After the 1st, 5th and 10th pulse, the participant was asked to rate his/her pain on the VNRS. The outcome measure for temporal summation is the difference between the tenth and the first VNRS score (24).

Endogenous pain inhibition: conditioned pain modulation

To assess conditioned pain modulation, temporal summation measures were taken while an occlusion cuff was inflated to a painful intensity and maintained at that level on the opposing (left) arm (as a heterotopic noxious conditioning stimulus). The cuff was inflated at approximately 20mmHg/s until the point the sensation first became painful (participants were instructed to say ‘stop’ at this point). Next, they adapted for 30 seconds to the stimulus and subsequently rated their pain on a VNRS. Cuff inflation was then increased or decreased until the participant indicated the pain level was equal to 3/10 on the VNRS. The left arm was then rested on a table and conditioned pain modulation was assessed by replicating the temporal summation assessment as described above. The outcome measure for conditioned pain modulation is the difference between the VNRS score from the first temporal summation pulse before cuff inflation and the VNRS score from the first temporal summation pulse when the arm was resting with the cuff inflated (24).

Statistical analysis

Participant characteristics were compared using Chi-squared and Kruskal-Wallis tests. Experimental pain measures were fitted as dependent variables in linear regression models, with group, age and sex as independent variables. Comparisons between the two patient groups were also adjusted for duration of illness. Pain pressure thresholds and cuff pressure thresholds yielded non-normal residuals and were log-transformed. For these two variables, we reported geometric means and estimated between-group percentage differences (as a difference ratio (DR)). For temporal summation and conditioned pain modulation, we reported arithmetic means and estimated between-group mean differences. We calculated pairwise correlation coefficients between the experimental pain measurements and each of the patient-reported measures, with evidence of correlation assessed by unadjusted and Bonferroni-adjusted P-values. All analyses were performed using Stata (StataCorp. 2013. Stata Statistical Software: Release 14. College Station, TX: StataCorp LP).

RESULTS

Participant characteristics

All groups were comparable for age (**Table 1**). Two MS patients had secondary progressive MS, one receiving treatment (Rebif®). The other 17 MS patients had relapsing remitting MS, with a median (IQR) interval between last relapse and experimental pain measurements of 55 (18-76) months. Of these 17 patients, 11 were receiving treatment (1 on Avonex®, 2 on Copaxone®, 2 on Gilenya®, 2 on Rebif®, and 4 on Tysabri®. There was a higher proportion (96%) of female patients in the CFS group, compared with the MS (68%) and control (64%) groups. Compared with MS patients, CFS patients had a longer disease duration (median 106 *vs* 60 months). A higher proportion of CFS patients (65%) were ‘professionally inactive’ (not in employment or education) compared with 26% of MS patients and 23% of healthy

controls. CFS patients had the lowest HRQOL scores, the highest fatigue, depression and pain scores, and the greatest impairment of concentration and physical activity (highest CIS scores). MS patients had lower motivation scores than CFS patients.

Experimental pain measurements

CFS patients had lower pain pressure thresholds than controls and MS patients (**Table 2**). Finger pain pressure thresholds of CFS patients were 12% lower compared with controls (difference ratio (DR)=0.88 (95% CI 0.74-1.05), p=0.15) and 25% lower compared with MS patients (DR=0.75 (0.59-0.95), p=0.02); shoulder pain pressure thresholds were 29% lower compared with controls (DR=0.71 (0.56-0.90), p=0.005) and 26% lower compared with MS patients (DR=0.74 (0.52-1.04), p=0.08).

Deep-tissue hyperalgesia measurements indicated pain experienced at 23% lower 2nd cuff pressure threshold for CFS patients compared with controls (DR=0.77 (0.59-1.00), p=0.05) and 41% lower 2nd cuff pressure threshold compared with MS patients (DR=0.59 (0.41-0.86), p=0.006). 1st cuff pressure threshold was 29% lower for CFS patients compared with MS patients (DR=0.71 (0.53-0.94), p=0.02), with weaker evidence of differences between CFS patients and healthy controls (DR=0.86 (0.70-1.07), p=0.17) and between MS patients and healthy controls (DR=1.23 (0.95-1.58), p=0.12).

Temporal summation measurements indicated that the greatest increase in pain (difference between 10^{th} and 1^{st} VNRS score) was in CFS patients (difference=1.88 (1.28-2.47)), followed by controls (difference=1.33 (0.91-1.76)) and then MS patients (difference=1.08 (0.43-1.72)). Compared with controls, temporal summation in fingers was higher in CFS patients (difference=0.57 (-0.13-1.27), p=0.11) and lower in MS patients (difference=-0.82 (-1.66-0.02), p=0.06), and there was particularly strong evidence for a difference between CFS and MS patients (difference=1.15 (0.33-1.97), p=0.006). There were no between-group

differences for temporal summation measured in shoulders, or for conditioned pain modulation measured at either site.

Correlations between experimental pain measurements and patient-reported characteristics

There were few consistent or strong pairwise correlations between experimental pain measurements and patient-reported characteristics (**Table 3**), with the SF-36 physical component score (higher score=higher functioning) tending to be positively correlated with higher pain thresholds (pain pressure and cuff pressure) and negatively associated with temporal summation in both patient groups, and CIS physical activity score (higher score=lower functioning) showing the same correlations but with opposite signs. Subjective fatigue severity also showed the same pattern in both patient groups, tending to be negatively correlated with higher pain thresholds and positively associated with temporal summation. Subjective pain in CFS patients was strongly negatively correlated with pain pressure thresholds and cuff pressure thresholds, and positively correlated with temporal summation. There were no strong correlations between subjective pain and experimental pain measurements in MS patients.

DISCUSSION

To our knowledge, this is the first study comparing experimental pain measurements between groups of CFS patients, MS patients and healthy pain-free controls. Our study has shown that there were greater differences between CFS and MS patients in some experimental pain measurements than between either patient group and controls. Specifically, we observed lower pain pressure thresholds (indicating widespread pressure hyperalgesia), lower cuff pressure thresholds (indicating deep-tissue hyperalgesia), and enhanced temporal summation

(indicating poorer functioning of endogenous pain facilitation) in fingers (but not in shoulders) in CFS compared with MS patients. There were no between-group differences in conditioned pain modulation, i.e. no differences in endogenous pain inhibition. These results show that overactive endogenous pain facilitation is characteristic of pain symptoms in CFS, but not in MS. This is consistent with central sensitization being the predominant pain type in CFS, but not in MS, although we cannot discount predominantly neuropathic pain in MS patients evolving over time to a state of predominant central sensitization pain as a result of abnormal central pain processing.

The presence of widespread hyperalgesia in people with CFS is not a novel finding (10,26,27), but this aspect of pain has only recently been reported in people with MS (12). The exact mechanisms underlying pain and widespread hyperalgesia in MS have not been elucidated. The presence of structural lesions in the central nervous system (the spinothalamic tract), causing increased neuronal excitability at the site of injury or at remote sites, resulting in a state of hyperexcitability (central sensitization) has been one hypothesis (28). By contrast with the findings of Fernández-de-las-Peñas *et al.* (12), we did not observe widespread pressure hypersensitivity in our study sample of MS patients. The presence of widespread pain hypersensitivity in people with MS may only be a feature of sensory disturbances related to damage affecting the somatosensory system and, in patients with predominantly neuropathic pain, endogenous pain facilitation and inhibition could be normal.

Our study follows on from two earlier studies which used the same patient groups (29,30). The first of these two studies showed that CFS patients scored higher on symptom severity and worse on handgrip strength, muscle recovery, and cognitive performance compared to MS patients and controls (29). Conditioned pain modulation efficiency represents an important brain-orchestrated inhibitory mechanism of pain processing (30), with higher

316 conditioned pain modulation values reflecting a more efficient pain inhibitory response.
317 Interestingly, in our study we found no differences in conditioned pain modulation either
318 between patients and controls or between CFS and MS patients. In the CFS group this result
319 is consistent with the study of Meeus *et al.* (31), who used the same conditioned pain
320 modulation assessment protocol as we did. However, in an earlier study using a different
321 protocol (immersion/withdrawal of the arm from warm water) , dysfunctional conditioned
322 pain modulation was identified in CFS patients compared with controls (13). These
323 contrasting results could be explained by the measurement method. Conditioned pain
324 modulation is a reliable psychophysiological measurement for studying endogenous
325 analgesia, but the degree of reliability is dependent on stimulation parameters and study
326 methodology (32). We used a combination of ischemic pressure and mechanical pressure
327 pain thresholds, whilst other studies have applied heat stimuli (13,33), cold water (34) or
328 electricity (35).The endogenous pain modulatory system has not been studied in detail in
329 relation to MS, and we are not aware of previous studies looking at the efficiency of the
330 conditioned pain modulation mechanism in people with MS. Svendsen *et al.* observed a
331 higher frequency of temporal summation (endogenous pain facilitation) in MS patients with
332 chronic pain compared to MS patients without chronic pain (36). Our study sample of people
333 with MS did not report significant pain complaints (29). Indeed, cuff pressure thresholds and
334 temporal summation in the MS group tended to indicate, albeit weakly, less pain than the
335 pain-free control group. By contrast, CFS patients reported quite high levels of subjective
336 pain, which was strongly correlated with experimental pain measures in CFS patients. It
337 could be argued that this between-group variation in ‘baseline’ subjective pain may explain
338 the differences that we observed in experimental pain measurements between CFS and MS
339 patients, but this would not explain why we found greater differences between CFS and MS
340 patients than between CFS patients and controls.

Pain is a multidimensional phenomenon and self-reported pain (pain perception) is undoubtedly influenced by patients' previous experiences and beliefs. Negative pain-related cognitions and beliefs are common in CFS, and we previously found significantly higher negative illness cognitions in the CFS group compared with the MS group (29), which may (in part) explain why self-reported pain was lower in our MS sample.

One strength of our study is that controls had to be inactive, because it is known that CFS patients, in general, have a more sedentary lifestyle (37). Hence, observed differences could not be due to a higher activity level of the control group. To ensure generalizability, CFS and MS patients were diagnosed according to established criteria, and MS patients were seen by a specialist neurologist. The main limitations of our study are its cross-sectional design and small samples, defined by earlier studies designed to investigate recovery of muscle function. We did not have data on the characteristics of patients who were not recruited or who did not wish to participate in the study hence, we were not able to assess the representativeness of our sample in relation to the respective patient populations. Asking patients to stop taking pain medication two weeks prior to the study may have introduced a selection bias into our patient groups if patients who experienced higher levels of pain felt unable to participate. The 2-week wash-out period for medications may not have been long enough for all types of drug, and might have introduced bias into our findings if, for example, analgesic medications and oral contraceptives inhibit conditioned pain modulation and were used differentially across the patient and/or control groups (38). Sex differences and longer disease duration in patients with CFS may partly explain the observed differences, although our estimates were adjusted for these variables.

CONCLUSION

Our results do not support the hypothesis that patients with CFS and MS, compared to controls, will present with poorer functioning of endogenous pain inhibition and/or with overactive endogenous pain facilitation. Instead, we found evidence only of enhanced endogenous pain facilitation in CFS compared with MS patients. Although pain is a commonly-reported symptom in both diseases, our results suggest that there are important differences in the underlying mechanisms, and experience, of pain in CFS and MS.

REFERENCES

1. Fukuda K, Straus SE, Hickie I, Sharpe MC, Dobbins JG, Komaroff A. The chronic fatigue syndrome: a comprehensive approach to its definition and study. International Chronic Fatigue Syndrome Study Group. *Ann Intern Med* 1994:121: 953-959.
2. Collin SM, Nikolaus S, Heron J, Knoop H, White PD, Crawley E. Chronic fatigue syndrome (CFS) symptom-based phenotypes in two clinical cohorts of adult patients in the UK and The Netherlands. *J Psychosom Res* 2016:81: 14-23.
3. Collin SM, Nuevo R, van de Putte EM, Nijhof SL, Crawley E. Chronic fatigue syndrome (CFS) or myalgic encephalomyelitis (ME) is different in children compared to in adults: a study of UK and Dutch clinical cohorts. *BMJ Open* 2015:5: e008830.
4. Benedict RH, Wahlig E, Bakshi R, Fishman I, Munschauer F, Zivadinov R, Weinstock-Guttman B. Predicting quality of life in multiple sclerosis: accounting for physical disability, fatigue, cognition, mood disorder, personality, and behavior change. *J Neurol Sci* 2005:231: 29-34.
5. Garg H, Bush S, Gappmaier E. Associations Between Fatigue and Disability, Functional Mobility, Depression, and Quality of Life in People with Multiple Sclerosis. *Int J MS Care* 2016:18: 71-77.
6. Fiest KM, Fisk JD, Patten SB, Tremlett H, Wolfson C, Warren S, McKay KA, Berrigan L, Marrie RA. Comorbidity is associated with pain-related activity limitations in multiple sclerosis. *Mult Scler Relat Disord* 2015:4: 470-476.
7. Branas P, Jordan R, Fry-Smith A, Burls A, Hyde C. Treatments for fatigue in multiple sclerosis: a rapid and systematic review. *Health Technol Assess* 2000:4: 1-61.
8. DeSousa EA, Albert RH, Kalman B. Cognitive impairments in multiple sclerosis: a review. *Am J Alzheimers Dis Other Demen* 2002:17: 23-29.
9. Foley PL, Vesterinen HM, Laird BJ, Sena ES, Colvin LA, Chandran S, MacLeod MR, Fallon MT. Prevalence and natural history of pain in adults with multiple sclerosis: systematic review and meta-analysis. *Pain* 2013:154: 632-642.
10. Meeus M, Nijs J. Central sensitization: a biopsychosocial explanation for chronic widespread pain in patients with fibromyalgia and chronic fatigue syndrome. *Clin Rheumatol* 2007:26: 465-473.
11. Nijs J, Meeus M, Van Oosterwijck J, Ickmans K, Moorkens G, Hans G, De Clerck LS. In the mind or in the brain? Scientific evidence for central sensitisation in chronic fatigue syndrome. *Eur J Clin Invest* 2012:42: 203-212.
12. Fernandez-de-Las-Penas C, Ortega-Santiago R, Ortiz-Gutierrez R, Caminero AB, Salom-Moreno J, Arendt-Nielsen L. Widespread pressure pain hypersensitivity in patients with multiple sclerosis with and without pain as sign of central sensitization. *Clin J Pain* 2015:31: 66-72.
13. Meeus M, Nijs J, Van de Wauwer N, Toeback L, Truijen S. Diffuse noxious inhibitory control is delayed in chronic fatigue syndrome: an experimental study. *Pain* 2008:139: 439-448.
14. Vase L, Nikolajsen L, Christensen B, Egsgaard LL, Arendt-Nielsen L, Svensson P, Staehelin Jensen T. Cognitive-emotional sensitization contributes to wind-up-like pain in phantom limb pain patients. *Pain* 2011:152: 157-162.
15. McDonald WI, Compston A, Edan G, Goodkin D, Hartung HP, Lublin FD, McFarland HF, Paty DW, Polman CH, Reingold SC, Sandberg-Wollheim M, Sibley W, Thompson A, van den Noort S, Weinshenker BY, Wolinsky JS. Recommended diagnostic criteria for multiple sclerosis: guidelines from the International Panel on the diagnosis of multiple sclerosis. *Ann Neurol* 2001:50: 121-127.

16. Kurtzke JF. Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). *Neurology* 1983:33: 1444-1452.
17. Bernstein MS, Morabia A, Sloutskis D. Definition and prevalence of sedentarism in an urban population. *Am J Public Health* 1999:89: 862-867.
18. Ware JE, Kosinki M, Keller S, D. *SF-36 Physical and Mental Health Summary Scales: A User's Manual*. The Health Institute, Boston MA, 1994.
19. Haywood KL, Staniszewska S, Chapman S. Quality and acceptability of patient-reported outcome measures used in chronic fatigue syndrome/myalgic encephalomyelitis (CFS/ME): a systematic review. *Qual Life Res* 2012:21: 35-52.
20. Vercoulen JH, Swanink CM, Fennis JF, Galama JM, van der Meer JW, Bleijenberg G. Dimensional assessment of chronic fatigue syndrome. *J Psychosom Res* 1994:38: 383-392.
21. Vercoulen JH, Alberts M, Bleijenberg G. The Checklist Individual Strength (CIS). *Gedragstherapie* 1999:32: 131-136.
22. Steer RA, Cavalieri TA, Leonard DM, Beck AT. Use of the Beck Depression Inventory for Primary Care to screen for major depression disorders. *Gen Hosp Psychiatry* 1999:21: 106-111.
23. Nijs J, Thielemans A. Kinesiophobia and symptomatology in chronic fatigue syndrome: a psychometric study of two questionnaires. *Psychol Psychother* 2008:81: 273-283.
24. Meeus M, Ickmans K, De Clerck LS, Moorkens G, Hans G, Grosemans S, Nijs J. Serotonergic descending inhibition in chronic pain: design, preliminary results and early cessation of a randomized controlled trial. *In Vivo* 2011:25: 1019-1025.
25. Vanderweeen L, Oostendorp RA, Vaes P, Duquet W. Pressure algometry in manual therapy. *Man Ther* 1996:1: 258-265.
26. Meeus M, Nijs J, Huybrechts S, Truijen S. Evidence for generalized hyperalgesia in chronic fatigue syndrome: a case control study. *Clin Rheumatol* 2010.
27. Meeus M, Roussel NA, Truijen S, Nijs J. Reduced pressure pain thresholds in response to exercise in chronic fatigue syndrome but not in chronic low back pain: an experimental study. *J Rehabil Med* 2010:42: 884-890.
28. Truini A, Galeotti F, La Cesa S, Di Rezze S, Biasiotta A, Di Stefano G, Tinelli E, Millefiorini E, Gatti A, Cruccu G. Mechanisms of pain in multiple sclerosis: a combined clinical and neurophysiological study. *Pain* 2012:153: 2048-2054.
29. Meeus M, Ickmans K, Struyf F, Kos D, Lambrecht L, Willekens B, Cras P, Nijs J. What is in a name? Comparing diagnostic criteria for chronic fatigue syndrome with or without fibromyalgia. *Clin Rheumatol* 2016:35: 191-203.
30. Ickmans K, Meeus M, De Kooning M, Lambrecht L, Pattyn N, Nijs J. Associations Between Cognitive Performance and Pain in Chronic Fatigue Syndrome: Comorbidity with Fibromyalgia Does Matter. *Pain Physician* 2015:18: E841-852.
31. Meeus M, Ickmans K, Struyf F, Hermans L, Van Noesel K, Oderkerk J, Declerck LS, Moorkens G, Hans G, Grosemans S, Nijs J. Does acetaminophen activate endogenous pain inhibition in chronic fatigue syndrome/fibromyalgia and rheumatoid arthritis? A double-blind randomized controlled cross-over trial. *Pain Physician* 2013:16: E61-70.
32. Kennedy DL, Kemp HI, Ridout D, Yarnitsky D, Rice AS. Reliability of conditioned pain modulation: a systematic review. *Pain* 2016:157: 2410-2419.
33. Moont R, Crispel Y, Lev R, Pud D, Yarnitsky D. Temporal changes in cortical activation during distraction from pain: a comparative LORETA study with conditioned pain modulation. *Brain Res* 2012:1435: 105-117.

34. Arendt-Nielsen L, Sluka KA, Nie HL. Experimental muscle pain impairs descending inhibition. *Pain* 2008:140: 465-471.
35. Oono Y, Wang K, Svensson P, Arendt-Nielsen L. Conditioned pain modulation evoked by a mechanical craniofacial stimulus is not influenced by noxious stimulation of the temporomandibular joint. *J Orofac Pain* 2012:26: 105-116.
36. Svendsen KB, Jensen TS, Hansen HJ, Bach FW. Sensory function and quality of life in patients with multiple sclerosis and pain. *Pain* 2005:114: 473-481.
37. Meeus M, van Eupen I, van Baarle E, De Boeck V, Luyckx A, Kos D, Nijs J. Symptom fluctuations and daily physical activity in patients with chronic fatigue syndrome: a case-control study. *Arch Phys Med Rehabil* 2011:92: 1820-1826.
38. Goubert D, Danneels L, Cagnie B, Van Oosterwijck J, Kolba K, Noyez H, Meeus M. Effect of Pain Induction or Pain Reduction on Conditioned Pain Modulation in Adults: A Systematic Review. *Pain Pract* 2015:15: 765-777.

Table 1: Demographic, clinical and patient-reported characteristics of participants

	HC (n=39)	MS (n=19)	CFS (n=48)	P-value[a]
Age (years), median (range)	40 (19 – 61)	40 (25 – 59)	41 (19 – 59)	P=0.56
Female, n (%)	25 (64.1%)	13 (68.4%)	46 (95.8%)	P<0.001
Body Mass Index (kg/m^2), median (IQR)	23.0 (20.3 – 28.6)	23.9 (21.1 – 25.8)	24.5 (20.8 – 27.4)	P=0.82
Disease Duration (months), median (IQR)	n/a	60 (16 – 288)	106 (8 – 864)	P=0.02
Occupational status 'inactive', n (%)	9 (23.1%)	5 (26.3%)	31 (64.6%)	P<0.001
Anti-depressant medication, n (%)	0 (0.0%)	1 (5.3%)	8 (16.7%)	P=0.01
Pain medication, n (%)	1 (2.6%)	0 (0.0%)	0 (0.0%)	P=0.55
SF-36 mental component (0-100), median (IQR)	85 (80 – 91)	76 (48 – 87)	52 (31 – 61)	P<0.001
SF-36 physical component (0-100), median (IQR)	89 (80 – 94)	62 (44 – 80)	32 (23 – 39)	P<0.001
CIS subjective fatigue severity, median (IQR)	20 (13 – 32)	38 (26 – 46)	52 (46.5 – 55)	P<0.001
CIS reduced concentration, median (IQR)	11 (5 – 19)	23 (19 – 26)	28 (25 – 32.5)	P<0.001
CIS reduced motivation, median (IQR)	8 (5 – 14)	14 (7 – 20)	12 (10 – 19)	P<0.001
CIS reduced physical activity, median (IQR)	7 (3 – 12)	12 (6 – 15)	15.5 (11 – 19)	P<0.001
BDI-PC, median (IQR)	1 (0 – 2)	1 (0 – 3)	2.5 (1 – 5)	P<0.001
Visual analogue subjective pain rating (0-100)	6 (0 – 16)	6 (0 – 27)	49 (22 – 66)	P<0.001

[a]Kruskal-Wallis test for medians, Fisher's exact test for proportions; SF-36 = Medical Outcomes Study 36-Item Short-Form Health Survey; CIS = Checklist Individual Strength; BDI-PC = Beck Depression Inventory for Primary Care

Table 2: Experimental pain measurements (mean (95% CI)) and between-group differences, comparing multiple sclerosis (MS) and chronic fatigue syndrome (CFS) patients with healthy controls and comparing CFS patients with MS patients[a]

	HC (n=39)	MS (n=19)	CFS (n=48)
Pain pressure threshold finger (kg/cm^2)	6.77 (6.08, 7.54)	7.63 (6.43, 9.06)	5.60 (4.92, 6.38)
Difference (ratio) comparing patients with HC[b]		1.12 (0.91, 1.38), p=0.28	0.88 (0.74, 1.05), p=0.15
Difference (ratio) comparing CFS vs MS[c]		0.75 (0.59, 0.95), p=0.02	
Pain pressure threshold shoulder (kg/cm^2)	3.78 (3.32, 4.31)	3.54 (2.80, 4.48)	2.47 (2.06, 2.96)
Difference (ratio) comparing patients with HC[b]		0.93 (0.70, 1.23), p=0.60	0.71 (0.56, 0.90), p=0.005
Difference (ratio) comparing CFS vs MS[c]		0.74 (0.52, 1.04), p=0.08	
1st cuff pressure threshold (mmHg)	167 (145, 193)	205 (177, 237)	135 (115, 157)
Difference (ratio) comparing patients with HC[b]		1.23 (0.95, 1.58), p=0.12	0.86 (0.70, 1.07), p=0.17
Difference (mean) comparing CFS vs MS[c]		0.71 (0.53, 0.94), p=0.02	
2nd cuff pressure threshold (mmHg)	131 (110, 155)	159 (128, 198)	88 (72, 107)
Difference (ratio) comparing patients with HC[b]		1.23 (0.89, 1.70), p=0.20	0.77 (0.59, 1.00), p=0.05
Difference (mean) comparing CFS vs MS[c]		0.59 (0.41, 0.86), p=0.006	
Temporal summation finger	1.62 (1.06, 2.17)	0.82 (0.40, 1.23)	2.20 (1.77, 2.63)
Difference (mean) comparing patients with HC[b]		-0.82 (-1.66, 0.02), p=0.06	0.57 (-0.13, 1.27), p=0.11
Difference (mean) comparing CFS vs MS[c]		1.15 (0.33, 1.97), p=0.006	
Temporal summation shoulder	1.33 (0.91, 1.76)	1.08 (0.43, 1.72)	1.88 (1.28, 2.47)
Difference (mean) comparing patients with HC[b]		-0.24 (-1.18, 0.69), p=0.61	0.34 (-0.43, 1.12), p=0.38
Difference (mean) comparing CFS vs MS[c]		0.34 (-0.78, 1.46), p=0.54	
Conditioned pain modulation finger	0.00 (-0.25, 0.25)	-0.29 (-0.90, 0.32)	-0.05 (-0.44, 0.33)
Difference (mean) comparing patients with HC[b]		-0.25 (-0.89, 0.38), p=0.43	0.03 (-0.50, 0.56), p=0.91
Difference (mean) comparing CFS vs MS[c]		0.31 (-0.49, 1.11), p=0.44	
Conditioned pain modulation shoulder	-0.03 (-0.43, 0.38)	-0.05 (-0.58, 0.47)	0.10 (-0.28, 0.49)
Difference (mean) comparing patients with HC[b]		-0.10 (-0.79, 0.59), p=0.77	-0.06 (-0.63, 0.51), p=0.84
Difference (mean) comparing CFS vs MS[c]		0.01 (-0.74, 0.76), p=0.97	

[a] Values shown for pain pressure thresholds and cuff pressure thresholds are geometric means, and differences between groups are relative differences, interpreted as % increase/decrease compared with HC, e.g. 1.25 = 25% higher, 0.75 = 25% lower. Values shown for temporal summation and **conditioned pain modulation** are arithmetic means, and differences between groups are absolute (mean) differences.

[b] Adjusted for age and sex

[c] Adjusted for age, sex and duration of illness

Table 3: Pairwise correlations between experimental pain measurements and patient-reported characteristics[a]

	Pain pressure threshold finger		Pain pressure threshold shoulder		1st cuff pressure threshold		2nd cuff pressure threshold		Temporal summation finger		Temporal summation shoulder		Conditioned pain modulation finger		Conditioned pain modulation shoulder	
	MS	**CFS**	**MS**	**CFS**	**MS**	**CFS**	**MS**	**CFS**	**MS**	**CFS**	**MS**	**CFS**	**MS**	**CFS**	**MS**	**CFS**
SF-36 mental component	0.29	0.08	0.27	0.04	0.26	0.18	0.31	0.14	-0.37	-0.16	-0.33	-0.06	-0.10	0.12	0.28	-0.03
SF-36 physical component	0.47*	0.23	0.34	0.31*	0.21	0.35*	0.34	0.29*	-0.29	-0.36*	-0.24	-0.23	-0.11	-0.01	0.09	-0.08
CIS subjective fatigue severity	-0.38	-0.28*	-0.35	-0.31*	-0.27	-0.20	-0.38	-0.22	0.26	0.34*	0.32	0.21	0.03	-0.18	-0.07	0.06
CIS reduced concentration	0.01	-0.07	0.09	-0.03	0.30	-0.07	0.04	-0.09	0.05	0.09	0.02	0.04	0.28	-0.01	-0.01	-0.10
CIS reduced motivation	-0.29	-0.07	-0.24	-0.07	0.07	-0.13	-0.19	-0.19	0.02	0.07	-0.25	0.11	-0.05	-0.04	-0.05	0.03
CIS reduced physical activity	0.03	-0.28*	0.09	-0.25	0.21	-0.23	-0.19	-0.17	0.04	0.42**	-0.07	0.29*	0.18	-0.21	-0.14	0.08
BDI-PC	0.03	-0.05	0.03	-0.02	-0.32	-0.15	-0.02	-0.17	0.31	-0.08	0.17	0.17	-0.12	-0.19	-0.22	0.04
Visual analogue pain rating	-0.42	-0.34*	-0.30	-0.33*	-0.29	-0.34*	-0.24	-0.50**	-0.05	0.49**	0.19	0.57**	-0.39	-0.10	0.19	0.12

[a] Pearson correlation coefficients, *P<0.05, **P<0.007 (Bonferroni-adjusted P<0.05); SF-36 = Medical Outcomes Study 36-Item Short-Form Health Survey; CIS = Checklist Individual Strength; BDI-PC = Beck Depression Inventory for Primary Care